REMARKS

Statement Of The Substance Of The Interview

Applicants thank Examiner Steele for the helpful telephonic interview on April 30, 2009 with Applicants' representatives, Jacqueline Benn and Eric G. Lee, during which the pending rejections under 35 U.S.C. § 102(e), pending rejections for obviousness-type double patenting, priority, and potential claim amendments were discussed.

Entry of this Statement Of The Substance Of The Interview into the file of this application is respectfully requested.

Claims

Claims 125, 126, 128, 131-138, and 142 are currently pending and under consideration. Claims 125 and 142 have been amended to clarify the present claimed invention.

In particular, claim 125 has been amended to correct the numbering for the enumerated Markush group Q and to recite that the hapten-carrier elicits anti-nicotine antibodies in a human. Claim 125 has also been amended to add an additional branch CJ 11.1. Support for CJ 11.1 can found in U.S. Patent Application No. 08/563,673, now U.S. Patent No. 5,760,184 (the "'184 patent"), filed November 28, 1995, for which priority is claimed. Branch CJ 11.1 [$CH_2YCO(CH_2)_nCOQ$] is encompassed by branch CJ 7.1 [$CH_2Y(CH_2)_nQ$], where Y is NH, n is 0; and Q is another branch represented by branch CJ 3 [$CO(CH_2)_nCOQ$], where n is 2. Support for branch CJ 11.1 can be found at, *inter alia*, the '184 patent at col. 14, lines 22-25 and 44-45 and in specification as originally filed on page 36, lines 12-15 and 33-34.

Claim 142 has been amended to recite, in relevant part, a pharmaceutical composition further comprising a pharmaceutically acceptable excipient. Support for amended claim 142 can be in the '003 patent at, *inter alia*, col. 19, lines 2-35; and col. 34, lines 41-42.

No new matter has been added by these amendments. Upon entry of the present amendments, claims 125, 126, 128, 131-138, and 142 will be pending in the present application.

Priority

Applicants contend that they are entitled to the priority benefit of U.S. Application No. 08/563,673 ("the '673 application"), now the '184 patent, for one or more of the pending claims.

Regarding the Examiner's allegation that the specification of the '673 application fails to adequately disclose branches CJ 1.3 or CJ 11, Applicants submit that in the Amendment filed January 26, 2009, claim 125 was amended to delete branch CJ 1.3. Therefore, the Examiner's allegation that the specification of the '673 application fails to adequately disclose branch CJ 1.3 is rendered moot. Applicants submit that the specification of the '673 application, now the '184 patent, fully supports branch CJ 11 as cited in the currently pending claims. The '184 patent explicitly discloses that Q can be "another 'branch' identified by its 'CJ' reference number" (col. 14, lines 44-45). Furthermore, the '184 patent explicitly discloses that "n is an integer" (col. 14, line 22). Thus, branch CJ 11 [$YCO(CH_2)_nCOQ$] is encompassed by branch CJ 7 [$Y(CH_2)_nQ$], where Y is NH, n is 0, and Q is another branch represented by branch CJ 3 [$CO(CH_2)_nCOQ$], where n is 2 (*see* the '184 patent, col. 14, lines 23-25 and 44-45). Accordingly, Applicants respectfully submit that the '184 patent fully supports branch CJ 11. *See* M.P.E.P. 2163(B) ("While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure").

Because the specification of the '673 application discloses nicotine and nicotine deriviative, and discloses branch CJ 11, Applicants submit that claims 125, 126, 128, 131-138, and 142 are supported by the '673 application and entitled to the November 28, 1995 filing date.

Information Disclosure Statement

The Examiner alleges that the Information Disclosure Statement (IDS) filed January 26, 2009 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each cited foreign patent document. Applicants acknowledge, with appreciation, Examiner's pointing out of Applicants' inadvertent ommission. Accordingly, Applicants submit herewith, a legible copy of each of the cited references B20-B26. Applicants submit that upon submission of a copy of references B20-B26, the IDS filed January 26, 2009 is in compliance with 37 C.F.R. § 1.98(a)(2).

Claim Rejections

I. There Is Written Description Support For The Claims

The Examiner has rejected claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that the specification does not provide support for the

Markush group Q (claim 125) or the limitation "pharmaceutically acceptable carrier" (claim 142).

Applicants submit that the support for the Markush group Q can be found in the '003 patent at, *inter alia*, col. 14, lines 27-57; and in the originally filed specification at page 114, line 33 to page 115, line 1; and page 119, lines 4-12.

As discussed previously, claim 142, as amended, does not recite "pharmaceutically acceptable carrier." Accordingly, the rejection of claim 142 is rendered moot.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejections of claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 112, first paragraph.

II. The Claims are Not Anticipated By U.S. Patent No. 6,054,127

The Examiner has rejected claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,054,127 (the "'127 patent"), which has an effective filing date of March 31, 1995 (*see* Office Action, page 7, line 4). Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132, in six counterparts, by the inventors of the instant application demonstrating that the '127 patent is not a reference by another and should not qualify as prior art under 35 U.S.C. § 102(e). Therefore, the rejection in view of the '127 patent should be withdrawn.

III. The Claims are Not Obvious Over U.S. Patent Nos. 5,164, 504 and 5,601,831

The Examiner has rejected claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,164,504 to Walling *et al.* ("Walling"), and U.S. Patent No. 5,601,831 to Green *et al.* ("Green"). The claimed invention is not obvious over the cited art because, alone or in combination, the cited art fails to suggest all the claim limitations. The claims, as amended, recite pharmaceutical compositions comprising nicotine or a nicotine derivative linked to a pseudomonas exotoxin carrier, and wherein said conjugate elicits a nicotine-specific antibody response in a human.

In its recent decision addressing the issue of obviousness, *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also*, Examination Guidelines for

Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-28. The Supreme Court stated that in determining obviousness, "a court must ask whether the improvement is more than a predictable use of prior art elements according to their established functions." *KSR*, 127 S.Ct. at 1740, 82 U.S.P.Q.2d at 1396. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

Walling, in fact, teaches away from claimed invention

Walling not only fails to suggest the claimed invention, but in fact teaches away from the claimed invention. Walling describes cotinine, a nicotine metabolite, as a hapten coupled to a carrier such as bovine serum albumin (BSA), used to raise *cotinine-specific* antibodies in experimental animals (*e.g.*, mice) for use in immunoassays (*see, e.g.*, Walling, col. 1, lines 1-15 and 26-42; col. 5, lines 56-68; col. 6, lines 22-27; col. 7, lines 12-22; and col. 17, line 42 to col. 19, line 39). By contrast, the claimed invention relates to a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a pseudomonas exotoxin, and wherein the hapten-carrier conjugate *elicits a nicotine-specific antibody response*. Moreover, the originally filed specification of the claimed invention discloses that BSA, the carrier taught in Walling, would be an undesirable carrier for purposes of raising antibodies in humans because, as a food protein consumed by humans, it would fail to induce an immune response in humans (*see* instant specification, page 29, lines 9-12). Therefore, Walling does not suggest a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a pseudomonas exotoxin, and wherein the hapten-carrier conjugate induces a *nicotine-specific* antibody response in a subject. Indeed, Walling even teaches away from the claimed invention because Walling points to the advantages of raising antibodies that detect cotinine, not nicotine, due to its much longer half-life than nicotine and the ease of detection of cotinine compared to nicotine (*see* Walling, col. 1, lines 28-35).

Claim 125 has been amended to include a functional limitation that the "hapten-carrier conjugate elicites nicotine-specific antibodies in a human." The Federal Circuit has

held that functional limitations are permissible and should be given effect. *See*, *Application of Geerdes*, 491 F.2d 1260, 1262-63 (Fed. Cir. 1974) ("*[E]very* limitation in the claim must be given effect rather than considering one in isolation from the others."); *see also*, *In re Swinehart*, 439 F.2d 210, 212 (C.C.P.A. 1971) ("In our view, there is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims."). The Federal Circuit has further clarified that a functional claim limitation is to be accorded patentable weight, to the extent the prior art is or is not capable of meeting that functional limitation. *See*, *In re Schreiber*, 128 F.3d 1473, 1478-79 (Fed. Cir. 1997). In numerous cases and decisions after *Schreiber* the court and board have upheld claims reciting a functional limitation where the prior art did not meet or was not capable of meeting that functional limitation. *See*, *Ex parte Urbahn*, 2009 WL 557051 (B.P.A.I. 2009); *Ex parte Rainer*, 2008 WL 163547 (B.P.A.I. 2008); *see also*, *Innova/Pure Water Inc. v. Safari Walter Filtration Sys., Inc.*, 381 F.3d 1111 (Fed. Cir. 2004). As discussed previously, Walling describes cotinine, a nicotine metabolite, as a hapten coupled to a carrier, which is used to elicit *cotinine-specific antibodies* (*see*, *e.g.*, Walling, col. 1, lines 1-15 and 26-42; col. 5, lines 56-68; col. 6, lines 22-27; col. 7, lines 12-22; and col. 17, line 42 to col. 19, line 39). By contrast, the claimed invention relates to a pharmaceutical composition comprising a hapten-carrier conjugate, wherein the hapten is a nicotine or nicotine derivative, which is used to elicit *nicotine-specific antibodies*. The hapten-carrier conjugate of Walling does *not* elicit nicotine-specific antibodies in a human. Thus, because Walling is incapable of meeting the functional limitation of the claimed invention, Applicants respectfully submit that the functional limitation is to be accorded patentable weight.

Art as a whole taught away from claimed invention

As of the instant invention's filing date, not only Walling, but the art as a whole taught away from using nicotine-carrier conjugates for inducing an antibody response against nicotine in a human subject. As explained in the instant specification, nicotine is a small molecule hapten that is non-immunogenic, making it unlikely that one of skill in the art would expect to be able to successfully use it in a pharmaceutical composition capable of eliciting an immune response in a human (*see* instant specification, page 19, lines 13-19; page 57, lines 31-35; and page 103, lines 32-34). Not only is nicotine non-immunogenic, it actually – and in contrast to cotinine – *suppresses* the immune response (*see* Geng *et al.*, "Effects of Nicotine on the Immune Response. I. Chronic Exposure to Nicotine Impairs

Antigen Receptor-Mediated Signal Transduction in Lymphocytes," Toxicol. Appl. Pharmacol. 135: 268-78 (1995) (reference C93 of the Supplemental IDS filed January 26, 2009), at Abstract and Discussion section at page 75, 3rd paragraph). Because of its immunosuppressive effects, the skilled artisan would have had even more reason to doubt that nicotine and nicotine derivatives could be used in a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a pseudomonas exotoxin, and wherein the hapten-carrier conjugate elicits a nicotine-specific antibody response in a human.

Therefore, Walling's disclosure of cotinine-BSA for the purpose of raising cotinine-specific antibodies in animals, alone and in view of the art, does not suggest to the skilled artisan a viable approach for inducing antibodies against nicotine in human subjects.

The combination of Walling and Green fails to obviate the claimed invention

Walling does not teach or suggest the use of a pseudomonas exotoxin as a carrier. The Examiner attempts to overcome this omission by citing Green. Green teaches the use of protein "e" and peptides having protein "e" epitopes for vaccination against nontypable and typable *H. Influenzae* (*see* Green, col. 1, lines 62-64). Green characterizes protein "e" as being especially valuable for vaccination against *H. Influenzae (see,* Green, col. 3; lines 15-18). Indeed, Green provides that protein "e" can be used as a carrier protein to confer or enhance immunogenicity of other antigens (see, Green, col. 11, lines 11-15). Green also teaches that when a haptenic peptide of protein "e" is used, it can be conjugated to an immunogenic carrier molecule such as tetanus toxin or toxoid, diphtheria toxin or toxoid, and any mutant forms of these proteins such as CRM_{197}; or exotoxin A of Pseudomonas, heat labile toxin of *E. coli*, and rotaviral particles (including rotavirus and VP6 particles) (*see* Green, col. 11, lines 16-25).

The conjugates of Green are distinct from the hapten-carrier conjugates of the instant invention. Protein "e" is an outer membrane lipoprotein of the bacteria *H. Influenzae*, having a molecular weight of about 28 kDa and an amino acid sequence as set forth in Figures 7A-7B (*see* Green, col. 1, lines 57-62; col. 3, lines 9-15; and Figures 7A-7B). Protein "e" is highly conserved and highly immunogenic, and elicits an immune response against different strains of nontypable *H. Influenzae* (*see* Green, col. 3, lines 18-33), which provides an effective response against infection by *H. Influenzae*. As described previously, nicotine is a small molecule hapten that has been shown to suppress the immune response. Thus, in

contrast to protein "e," nicotine is not a peptide or protein and is not immunogenic. Additionally, Green describes the use of carriers such as pseudomonas exotoxin only in the context where the protein "e" or peptides having protein "e" epitopes are administered as multivalent subunit vaccines in combination with *other* antigens of *H. Influenzae* (*see* Green, col. 11, lines 34-39). One embodiment of such a multivalent subunit vaccine is where protein "e" or a peptide having protein "e" epitopes is administered in conjunction with *other* outer membrane proteins of *H. Influenzae* in order to achieve synergistic bactericidal activity (*see* Green, col. 11, lines 44-48; and claim 9). That is, Green teaches the use of pseudomonas exotoxin in a multivalent subunit vaccine where an immune response is induced against a plurality of different antigens of *H. Influenzae*. By contrast, the hapten-carrier conjugates of the instant invention elicit an immune response to a single antigen, *i.e.*, nicotine. Therefore, the conjugates of Green are distinct from the hapten-carrier conjugates of the instant invention.

Thus, neither Walling nor Green, alone or combined, describes a composition comprising nicotine, or a nicotine derivative, and pseudomonas exotoxin that elicits a nicotine-specific antibody response in humans.

The claimed invention possesses unexpected advantageous properties

The claimed invention is not rendered obvious by the cited art, in part, because the cited art, taken alone or in combination, fails to describe or suggest all of the claim limitations. *Graham*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Thus, the Examiner has failed to establish a case of *prima facie* obviousness. However, assuming *arguendo*, that a *prima facie* case of obviousness has been made, the Applicants invite the Examiner's attention to the unexpected advantageous and/or superior properties associated with the claimed conjugates. (A *prima facie* case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Chupp*, 816 F.2d 643, 646; 2 U.S.P.Q.2d 1437, 1439 (Fed Cir 1987)). NicVAX is an example of a nicotine derivative-pseudomonas exotoxin conjugate formulated as an anti-nicotine vaccine that is currently in clinical trials for smoking cessation in humans.

The Phase II clinical trials for NicVAX show that the nicotine-pseudomonas exotoxin conjugate vaccine induces a nicotine-specific antibody response (*see* Hatsukami *et al.*, "Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers" Clin. Pharmacol. Ther. 76: 456-67 (2005) (reference C82 of the Supplemental IDS filed June 12,

2008)). The trials show a clear dose response relationship between dose of nicotine conjugate vaccine and mean concentration of nicotine-specific antibodies in serum (*see*, Hatsukami *et al.*, at page 464, right col., first full paragraph, and Figures 1 and 3). This study demonstrated that 6 out of 16 patients who received the vaccine at a dose of 200 μg were able to abstain from smoking cigarettes for at least 30 days during the study, as compared to 2 out of 23 patients that received placebo. These clinical trial results indicate that nicotine conjugated to a pseudomonas exotoxin carrier can be used efficaciously as a vaccine to elicit an antibody response to nicotine to treat nicotine addiction. Thus, these clinical trial results support the unexpected advantageous properties associated with the claimed conjugates.

Accordingly, reconsideration and withdrawal of the rejection of claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 103(a) as being obvious over Walling and Green is respectfully requested.

IV. Double Patenting

The Double Patenting Rejection Of Claims 125, 126, 128, 131-138, And 142 Over Claims 1-18 Of Walling Alone Or In Combination With Green Should be Withdrawn

Claims 125, 126, 128, 131-138, and 142 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-18 of Walling, alone or in combination with Green.

The analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of the 35 U.S.C. § 103 obviousness determination (*see* M.P.E.P. § 804IIB1; *see In re Braat*, 937 F.2d 589 (Fed. Cir. 1991)). Accordingly, the factual inquiries set forth in *Graham*, 383 U.S. 1 (1966) that are employed for determinations of obviousness under 35 U.S.C. § 103 are also employed for obviousness-type double patenting rejection analysis (*see* M.P.E.P. § 804IIB1). As discussed above, Walling, alone or combined with Green, does not render obvious the claimed invention and the claimed invention is patentably distinct from the invention described in Walling, alone or in combination with Green. Accordingly, Applicants respectfully request that the double patenting rejection of claims 125, 126, 128, 131-138, and 142 over claims 1-18 of Walling, alone or in combination with Green, should be withdrawn.

The Double Patenting Rejection Of Claims 125, 126, 128, 131-138, And 142 Over Claims 88, 90, 103, 106, 108, 109, And 128-135 Of Application No. 11/472,215 Should Be Held In Abeyance

Claims 125, 126, 128, 131-138, and 142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 88, 90, 103, 106, 108, 109, and 128-135 of U.S. Application No. 11/472,215. During our April 30, 2009 telephonic interview, the Examiner indicated that since Application No. 11/472,215 is still pending, upon a finding of allowable subject matter, this application will be allowed to issue.

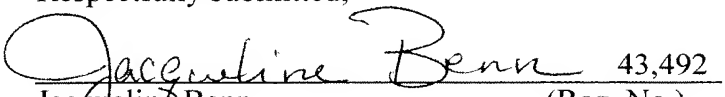
The Double Patenting Rejection Of Claims 125, 126, 128, 131-138, And 142 Over Claims 119-135 Of Application No. 11/472,220 Should Be Held In Abeyance

Claims 125, 126, 128, 131-138, and 142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 119-135 of U.S. Application No. 11/472,220. During our April 30, 2009 telephonic interview, the Examiner indicated that since Application No. 11/472,220 is still pending, upon a finding of allowable subject matter, this application will be allowed to issue.

CONCLUSION

Applicants respectfully request that the Examiner consider the amendments and the remarks made herein, and that the Examiner enter them into the record for the present application. Withdrawal of all rejections and an allowance is earnestly sought. The Examiner is invited to contact the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: June 11, 2009  43,492

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